## REMARKS

The Examiner's thoughtful attention to this application is sincerely appreciated.

**The Amendments**

The Specification, Claims and Abstract have been extensively amended, as indicated above.

The Specification has been amended to include the headings suggested by the Examiner.[1]

Claim 1 has been amended to specify that the method is applicable to "epithelial" cancer, to provide antecedent basis in step © for the term "DNA" in step (d), and to positively recite in step (e) the step of "making" the prognosis by ... and by adding the definition that the losses or mutations "are indicative that said resected tissue is in the progression pathway to development of invasive cancer."

The substantive amendments to Claim 1 have ample support in the original specification. The amendment inserting the term "epithelial" is made without prejudice to asserting broader

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[1] Because this caused major changes in the pagination of the Specification, the complete amended specification is included in this Response. For purposes of clarity, the pagination of the amended specification (tops of pages)is independent from the pagination of this Response (at the bottoms of pages).

definitions of the types of cancer in appropriate continuing applications. The term is supported at page 16, line12 of the original specification. The definition "progression pathway ... cancer" definition is supported at page 1, line 18, line 23 of the original specification.

## The Objections

The objection to the layout of the Specification has been cured by inserting the suggested headings.

The objection to the usage of the trademark has been cured by capitalizing it and adding the registered trademark symbol "®."

The objection based on multiple use of "Example 1" has been cured by deleting the reference to it on page 6 of the original specification.

## Claim Rejections

**Under 35 USC §112, First Paragraph:**

At the outset, neither the statutes, the regulations nor the case law prohibits claims covering an invention, the practice of which requires some "experimentation." Rather, the prohibition is against "**undue**" experimentation.

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. (*In re Wands*, 858 F.2d at 737)(emphasis added).

Fortunately, in the present case no experimentation at all required:

> The use of toluidine blue O dye and other dyes that selectively stain and thus, identify, cancerous tissue is notoriously old and well known. Even the cancer-selective staining mechanism (mitochondrial staining) has been documented and explained in the patent literature (US 6,649,144). In any event the procedure for the staining step is thoroughly described in the original specification (pages 5-10 and 12-16).
>
> Moreover, the "genetic analysis" of suspect tissue to detect whether there are molecular markers in the tissue which yield a diagnosis or prognosis of cancer is also old, well known and documented in the literature for example, in the papers cited at page 4 of the original specification and in issued patents (e.g., see US Patents 5,561,041; 5,726,019; 5,856,094; 5,935,787; 6,025,127; 6,235,470; 6,291,163; 6,479,234; 6,780,592 and references cited therein.)

Claim 1 claims the combination of these two steps, each of which is well-known separately: the selective staining step (paragraphs (a) and (b)) and the genetic alteration analysis step (paragraphs ©, (d) and (e)). Thus, Applicant respectfully asserts that the facts in the present case easily meet the requirements of *In re Wands:*

> Wands's disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time the application was filed, and all of the methods needed to practice the invention were well known. (858 F.2d at 840)(emphasis added)

**Under 35 USC §112, Second Paragraph**:

The Examiner's understanding of "resecting" is correct, i.e., to remove tissue as in tissue biopsy. See, e.g., the definition of "resect" in the Medterms.com dictionary:

> **Resect:** To remove. Resect and excise are not synonymous. Excise implies total removal whereas resect need not. A surgeon may resect part or all of a tumor but if the surgeon excises the tumor, all of the tumor is removed. From the Latin resectus, from resecare, meaning to trim, prune, cut back.

<http://www.medterms.com>

(a) The lack of proper antecedent basis in "the final step (d) for 'determining whether DNA extracted ..." is not understood as that language appeared in step (e) or original Claim 1. In any event, the original Claim 1 has been extensively amended to provide clear antecedent basis ("having DNA," "having said DNA" and "extracting said DNA") for the final step (e) recitation "determining whether DNA extracted ...".

(b) Amended Claim 1 now recites a final method step ("making a prognosis ...") that clearly relates back to the preamble. The original Claim 1 was not intended to be directed to a method of determining allelic losses, etc., but, rather to the method for early prediction ... .

**The Rejection Under 35 USC §103**

**The prior art problem of the Mashberg-type staining protocol** was that it was perceived (even by Mashberg himself) as having high rate of "false positives." In fact, Mashberg's issued US Patent 4,321,251 was specifically directed (Col 1, lines 68-42) to reducing the number of false positives. That problem persisted, as indicated by US Patent 5,372,801 to Tucci et al., which sought to avoid the complexity of the procedure of Mashberg '251 for reducing false positives (Col 1, line 67– Col 2, line 6). There was not even a consensus as to the reason for "false positives" or the mechanism of staining. For example, the US Patent 5,882,627 reported that the selective staining was due to the ability of the dye to penetrate normally tight intracellular junctions in cancerous tissue, while Tucci '801 attributed false positives to "non-specific staining" of mucosal tissue and, finally, the true mechanism of selective dye staining was disclosed as mitochondrial staining in US Patent 6,649,144. None of the prior workers had any idea that the vast proportion of reported "false positives" were **not in fact false**. (See original Specification, page 20, lines 18 et seq.)

**The prior art problem with the genetic alteration analysis protocol** was that one had to wait until there was visual indication, e.g., a lesion, to know where to take a tissue sample for genetic analysis, i.e., **after the tissue had already progressed to cancer**. Alternatively, analysis of body fluids would detect possible cancer or precancer, but, again, one could not tell where to take a tissue sample for genetic analysis or regular histological examination.

However, by combining these two protocols, one obtains immediate direction as to where to take the tissue sample and an immediate forecast ("prognosis") that cancer may develop, even before there is any visual indication of it. A full 80% of the samples identified by selective dye staining are "clonal" – **including those previously thought to be "false positives"** – and are, therefore, in the progression pathway to cancer and 50-75% of these samples will progress to invasive cancer. (Original Specification, pp. 18-19).

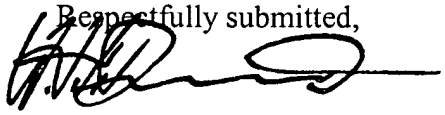
These protocols (and their respective disadvantages and problems) had existed side-by-side in the art for years, until Applicant made the connection here disclosed and asserted in amended Claim 1. By the claimed method, genetic moleclular analysis, with its huge advantage over conventional histology – – prognosis vs. after-the-fact diagnosis – – can now become mainstream.

It is respectfully urged that the foregoing objective evidence clearly rebuts the prima facie case of obviousness proposed by the Examiner

## CONCLUSION

For the foregoing reasons and in light of the above amendments, the Examiner is respectfully requested to reconsider the objections and rejections stated in the Office Action.

Respectfully submitted,



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